# Mitochondrial Disorders: Analysis of Their Clinical and Imaging Characteristics

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**PURPOSE:** Investigation of the clinical, imaging, and in vivo MR spectroscopy (MRS) characteristics of disorders of mitochondrial function. **METHODS:** Clinical, imaging (five CT and 20 MR examinations), and MRS (six studies in five patients) findings in 19 patients with mitochondrial disorders were retrospectively reviewed. Results were critically analyzed and, when applicable, compared with results in the literature. **RESULTS:** Patients included four with mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), two with myoclonus, epilepsy, and ragged red fibers (MERRF), two with Kearns-Sayre syndrome, seven with Leigh syndrome, one with progressive cerebral poliodystrophy (Alpers syndrome), and three with trichopoliodystrophy (Menkes disease). MELAS, MERRF, and Kearns-Sayre tended to occur in older children and adults, whereas Leigh syndrome, Alpers syndrome, and Menkes disease occurred in infants and young children. All diseases involved gray matter early in their course, manifest primarily as T2 prolongation, with the deep cerebral nuclei being involved more often than the cerebral cortex. When T2 prolongation was seen in the white matter (MELAS, MERRF, Kearns-Sayre, Leigh), the peripheral and retrotrigonal white matter showed early involvement. Patients with Menkes disease showed rapidly progressive atrophy accompanied by large subdural hematomas. Proton MRS showed an elevated lactate level in involved regions of the brain; the lactate peak disappeared in old areas of T2 prolongation. **CONCLUSIONS:** Mitochondrial disorders have a wide range of both clinical and imaging findings. Although no one set of findings is diagnostic of these disorders, the combination of deep gray matter involvement and peripheral white matter involvement in young adults or children should suggest the diagnosis, especially when associated with an elevated lactate level on proton MRS.

**Index terms:** Brain, diseases; Brain, occipital lobe; Brain, magnetic resonance; Brain, computed tomography

AJNR 14:1119–1137, Sep/Oct 1993

The mitochondrial disorders are a group of diseases characterized by disorders of mitochondrial function that result in impaired cellular adenosine triphosphate (ATP) production in affected cells (1–5). Single or multiple organs can be involved, with the striated muscles and brain most commonly affected (1–5). Mitochondrial disorders have been divided into somewhat ill-defined categories on the basis of their phenotypic, histologic, biochemical, and genetic manifestations. Some reasonably well-defined disorders include: myoclonus, epilepsy, and ragged red fibers (MERRF); mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); chronic external ophthalmoplegia plus chronic external ophthalmoplegia with retinal pigmentary abnormalities and abnormalities of multiple other systems (Kearns-Sayre syndrome); Leber hereditary optic neuropathy; progressive infantile poliodystrophy (Alpers disease); and subacute necrotizing encephalomyelitis (Leigh disease). We have had the opportunity to review magnetic resonance (MR) scans of 19 patients with many of the identified mitochondrial disorders. The purpose of this project was to document the characteristic MR and x-ray com-

Received August 21, 1992; revision requested October 6; revision received October 16 and accepted October 27.

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AJNR 14:1119–1137, Sep/Oct 1993 0195-6108/93/1405-1119

puted tomography (CT) findings in this group of patients and, when possible, to correlate these findings with the biologic bases for the disorders.

## Patients and Methods

The imaging characteristics of 19 patients with mitochondrial disorders were retrospectively reviewed. The patients included four with MELAS syndrome, two with Kearns-Sayre syndrome, two with MERRF, seven with Leigh disease, one with Alpers disease, and three with Menkes disease. A diagnosis was established by clinical findings in association with ragged red fibers and abnormal mitochondria upon muscle biopsy (and brain biopsy in patient 3) in the patients with MELAS and MERRF (2), by clinical criteria (2, 5, 6) in the patients with Kearns-Sayre syndrome, by autopsy in the patient with Alpers disease and the patient with Leigh disease, by typical clinical and radiologic findings and by biochemical analysis of cultured fibroblasts (6–9) in six patients with Leigh disease, and by abnormal levels of copper and ceruloplasmin in serum in the patients with Menkes disease. Summaries of clinical presentations in this series are listed in Table 1. Age ranges in the groups of patients at the time of their initial imaging studies were as follows: MELAS, 6 to 29 years; MERRF, 35 to 39 years; Kearns-Sayre, 13 to 18 years; Leigh disease, 3 months to 8 years; Alpers disease, 4 months; and Menkes disease, 1 to 5 months. Many of the older patients had been symptomatic for many years before the initial imaging study was obtained.

CT examinations, performed in five cases, consisted of contiguous axial 5-mm sections through the entire brain before and after the intravenous administration of iodinated contrast. The studies were assessed for size and attenuation of the gray and white matter structures of the brain by an experienced neuroradiologist (AJB). White matter atrophy was defined as an "Evans ratio" (greatest width of the frontal horns of the lateral ventricles divided by the internal diameter of the skull at that level [10, 11]) of more than 0.35. Cortical atrophy was subjectively diagnosed by the presence of enlarged cortical sulci. Areas of both increased and decreased attenuation were noted.

MR examinations consisted of sagittal 3- to 5-mm (1-mm "gap") spin-echo (SE) 500–600/11–20/1 (TR/TE/excitations) images, axial 4- to 5-mm SE 2000–3000/30–60, 70–120 images, and in two patients, coronal 5-mm SE 600/20 images. The images were evaluated for abnormal signal intensity and quantity of gray matter and white matter. Cortical gray matter thickness was measured from the hard copies of the films, and a thickness of less than 3 mm was considered abnormal (12). In addition, the state of myelination was assessed in patients younger than 4 years of age (13). Gadolinium-DTPA (0.1 mmol/kg) was infused intravenously in one patient (patient 3) with MELAS before the acquisition of 5-mm axial SE 600/11 images.

Proton MR spectroscopy (MRS) was performed at 1.5 T by the same system as was used for the MR imaging studies. Two sets of data were acquired in each of the four patients studied: one set was acquired from an area of brain with T2 prolongation on imaging studies; the other set was acquired from a similar area without apparent abnormality on the imaging study. Spectra were obtained from volumes of approximately 8 $cm^3$. The voxel was prescribed from T2-weighted axial MR images obtained in an imaging sequence during the same examination. A stimulated echo sequence (14, 15) combined with chemical shift-selective pulses was used for localization and water suppression, yielding a signal only from the region of interest at the spatial intersection of three section selective pulses. Field homogeneity was optimized from the localized volume by shimming of the water proton signal (water line widths after shimming were usually 8 to 10 Hz). After the shimming process, a chemical shift-selective excitation type sequence was used to suppress the unwanted water signal (by a factor of up to 1000). The water suppression pulse did not appear to distort appreciably the remainder of the observed spectra. One hundred averages (2000/20, 10.7) were obtained to achieve an adequate signal-to-noise ratio. Spectra were acquired with a standard imaging quadrature head coil.

**TABLE 1: Summary of clinical presentations**

| |
|---|
| MELAS (4) |
| Hemiparesis (4) |
| Hemianosia (2) |
| Seizures (2) |
| MERRF (2) |
| Myoclonus (2) |
| Seizures (2) |
| Ataxia (2) |
| Optic atrophy (1) |
| Hearing loss (1) |
| Proximal limb weakness (2) |
| Kearns-Sayre (2) |
| Ophthalmoplegia (2) |
| Retinal degeneration (2) |
| Ataxia (2) |
| Heart block (2) |
| Elevated cerebrospinal fluid protein (2) |
| Leigh disease (7) |
| Hypotonia (6) |
| Nystagmus (5) |
| Failure to thrive (3) |
| Respiratory difficulties (3) |
| Ataxia (4) |
| Developmental delay (6) |
| Alpers disease (1) |
| Seizures |
| Blindness |
| Hypotonia |
| Liver dysfunction |
| Menkes disease (3) |
| Hypothermia (3) |
| Hypotonia (3) |
| Seizures (3) |
| Failure to thrive (3) |
| Poor feeding (3) |
| Coarse, sparse hair (3) |

Note—Numbers in parentheses indicate number of patients.

Total examination time, including shimming, for the acquisition of spectra from the two separate voxels was about 20 minutes. The spectra obtained early in our experience were displayed graphically, with the abscissa displaying magnitude of pure absorption and the ordinate displaying frequency of the absorption in kilohertz. As the numerical value of the absorption in kilohertz changes, dependent upon the magnetic field strength, more recent spectra displayed frequency in parts per million, which does not change with field strength. The water peak was arbitrarily assigned a value of zero.

## Results

### *Clinical*

Table 1 gives a summary of the signs and symptoms of the patients in the study. Presentations were typical for the disorders.

### *Imaging*

A summary of the findings on imaging studies is found in Table 2.

Patients 1 through 4, all with MELAS, had unilateral or bilateral areas of abnormal tissue, primarily involving the posterior temporal, parietal, and occipital lobes (Fig 1) in three patients and the putamina in one (Fig 2). Low attenuation was seen on CT, and prolonged T2 relaxation was seen on MR in the involved regions. Patient 1 had bilateral occipital involvement, whereas patient 2 had unilateral parietal and occipital involvement. Both cortex and subcortical white matter were involved, although in patient 3, the white matter seemed more involved than the gray (Fig 1A). The involved areas crossed vascular boundaries in some patients but not in others. MR images were obtained four days after an acute exacerbation of symptoms (hemiparesis and ataxia) in patient 3 (Fig 1D). A new area of involvement showing T2 prolongation and heterogeneous enhancement was seen in the medial posterior frontal and parietal lobes, adjacent to the posterior temporal and occipital regions of the involvement noted previously. Patient 4 had two MR scans, the first at the time of presentation with left hemiparesis at age 13 and the second after the onset of right hemiplegia at age 17. The first scan (Fig 2A and B) showed prolonged T1 and T2 in the entire right putamen with sparing of the remainder of the brain. The second scan (Fig 2C) showed prolonged T1 and T2 and slight enlargement of the posterior half of the left putamen with persistent T1 and T2 prolongation with mild atrophy of the right putamen. Prominent sulci, suggestive of cortical atrophy, were noted in all four patients, most prominently in patient 1.

Patients 5 and 6, both with MERRF, showed diffuse cortical and white matter loss, leading to diffusely prominent sulci and ventricles (Fig 3). T2 prolongation was present in the periventricular white matter, particularly in the regions dorsal to the trigones and in the subinsular regions (Fig 3C). In addition, patient 6 had prolonged T2 in the cerebellar dentate nuclei and a small area of calcification in the right globus pallidus (Fig 3A and B).

Both patients 7 and 8, who had Kearns-Sayre syndrome, had areas of T2 prolongation in their cerebral subcortical white matter, globi palladi, thalami, dorsal brain stem, substantia nigra, and cerebellar white matter (Fig 4). The periventricular white matter was spared in both cases. The thalami were more affected than the globi palladi in patient 7, and the globi palladi were more involved in patient 8.

The seven patients with Leigh disease (patients 9 through 15) showed a spectrum of findings; however, all studies were characterized by the presence of T2 prolongation in the putamina bilaterally (Figs 5 through 7). A single patient with sequential studies 6 months apart showed progression of the putaminal changes, manifest as more extensive T2 prolongation and shrinkage of the putamina, and the development of T2 prolongation in the caudate heads bilaterally (Fig 5). Six patients had involvement of the caudates, three patients had involvement of the substantia nigra (Fig 6B), two had involvement of the dorsal midbrain in the region of the aqueduct (Fig 6B), two had delayed myelination (Fig 5), two had involvement of the dorsomedial medulla (Fig 6C), and one each had involvement of the bilateral thalami, of the frontal and insular cortex, and of the dorsal pons. One patient had demyelination (proved at autopsy) of the cerebral white matter (diffusely, Fig 7).

Patient 16, who had Alpers disease, showed a diminished volume of white matter and delayed myelination diffusely (Fig 8A). In addition, cortical thinning was present, most severely in the frontal, posterior temporal, and occipital lobes (Fig 8B and C).

Patients 17 through 19, all with Menkes disease, had scans that were remarkable for rapid progression of atrophy. Early scans, at ages 2 months and 1 month in patients 18 and 19 (Fig 9A), respectively, showed little abnormality. Both

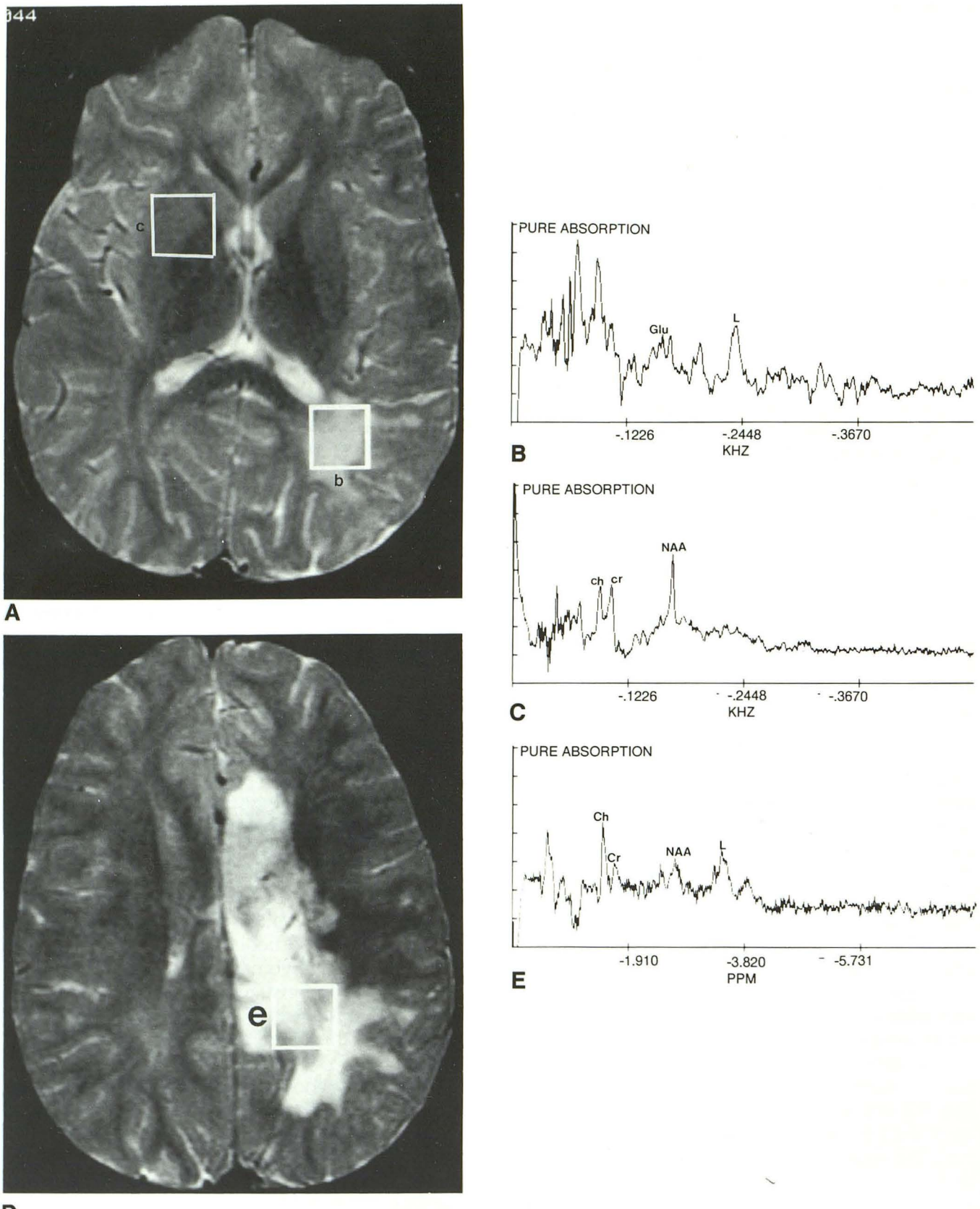


Fig. 1. Patient 3, 6 years old with MELAS.

*A*, Axial SE 2500/80 image shows T2 prolongation in the left temporo-occipital region (under box *b*). The high signal is not in a vascular distribution and spares the overlying cortex, which is of normal thickness. The spectrum shown in *B* is from box *b*. The spectrum in *C* is from box *c*.

scans revealed areas of shortened T1 in the cerebral cortex, particularly in the insular region, and a mild increase in the size of the cortical sulci. The later scans, obtained at ages 5 months (patient 17 and 19 [Fig 9B]) and 10 months (patient 17), showed profound atrophy of all structures, with enlarged ventricles and thin cortex. Large subdural hematomas were present in patients 17 and 19 (Fig 9B), presumably resulting from the cortex shrinking away from the calvarium and the known abnormally elongated intracranial vessels (16).

### *Spectroscopy*

Proton MRS was obtained in five patients, including three with Leigh disease and two with MELAS (patients 3 and 4). In all patients, a lactate peak (a characteristic doublet located −0.2 kHz (−3.4 ppm) upfield from water at 1.5 T) was present in some portions of the brain but was largest at the areas of acute or subacute processes, areas that generally had T2 prolongation. Thus, the lactate peak was largest in the lentiform nuclei in the patients with acute exacerbations of Leigh disease (Fig 6E) and in the affected (left) occipital and parietal lobes in patient 3, who had an exacerbation of MELAS (Figure 1). Interestingly, the spectra of patient 4, performed at the time of the second MR scan, showed increased lactate in the acutely involved posterior left putamen (even in the part of the putamen without prolonged T2; Fig 2E), but not in the chronically involved and atrophic-appearing right putamen (Fig 2D).

## Discussion

The mitochondrial disorders are a complex group of diseases, the origins of which have only recently begun to be understood. The classification (Table 3) and even the nomenclature of the disorders are still disputed by those most authoritative in the field (2–4, 17–19). The problems in the classification of the disorders lie in the complexity of mitochondrial metabolism (20), the unique characteristics of mitochondrial inheritance (21), and the normal deterioration of mitochondrial function with aging (5, 22, 23). A brief review of these subjects is essential to understanding these diseases and the controversies surrounding them.

### *Mitochondrial Metabolism*

Mitochondrial metabolism can be separated into four main steps (5, 20): 1) the transport of anions and neutral metabolites across the inner mitochondrial membrane by translocases; 2) the oxidation of pyruvate (pyruvate dehydrogenase enzyme complex) and fatty acids ($\beta$ oxidation); 3) the oxidation of acetyl-coenzyme A (Krebs cycle); and 4) the oxidation-reduction reactions (oxidative phosphorylation) in which the reducing equivalents generated in step 3 are channeled through the mitochondrial electron transport chain ultimately to liberate energy in the form of ATP. (Some people consider the liberation of ATP as a separate step and, therefore, break the process into five steps [2].)

A simple solution to the classification of mitochondrial diseases might be to establish four (or five) classes based on these steps. However, the same dysfunction can result from a primary substrate deficiency or from a defective mitochondrial membrane that retards the transport of that substrate into the mitochondria. The first situation may be considered a secondary, as opposed to primary, mitochondrial disorder; some authors, therefore, would exclude it from the classification of "true" mitochondrial disorders (2, 8, 24, 25). Moreover, abnormalities of different parts of the mitochondrial respiratory chain can result in the same phenotypic disease, whereas identical genetic defects sometimes cause different phenotypic manifestations (2, 4, 5, 26–28). This latter point will be elaborated upon in the following section on genetic considerations.

One source of this confusion lies in the fact that some of the polypeptides (proteins) that

*B*, Proton MRS from area of box *b* in *A* shows low N-acetyl aspartate (NAA) peak (not marked) and high lactate doublet (*L*) at −0.2 kHz. The NAA peak is poorly separated from the glutamate/glutamine/amino acid peaks (*Glu*) adjacent to it.

*C*, Proton MRS from area of box *c* in *A* shows a normal spectrum, with normal ratios of NAA, creatine-phosphocreatine (*cr*), and choline (*ch*).

*D*, Axial SE 2500/80 image at the time of an exacerbation of symptoms shows a new area of T2 prolongation in the medial posterior frontal and parietal regions. Both gray and white matter are involved. The white box *e* shows the location from which the spectrum in *E* was obtained.

*E*, Proton MRS from the voxel depicted in *D*. NAA and creatine/phosphocreatine are markedly reduced. A peak at −3.4 ppm (*L*) likely represents lactate.

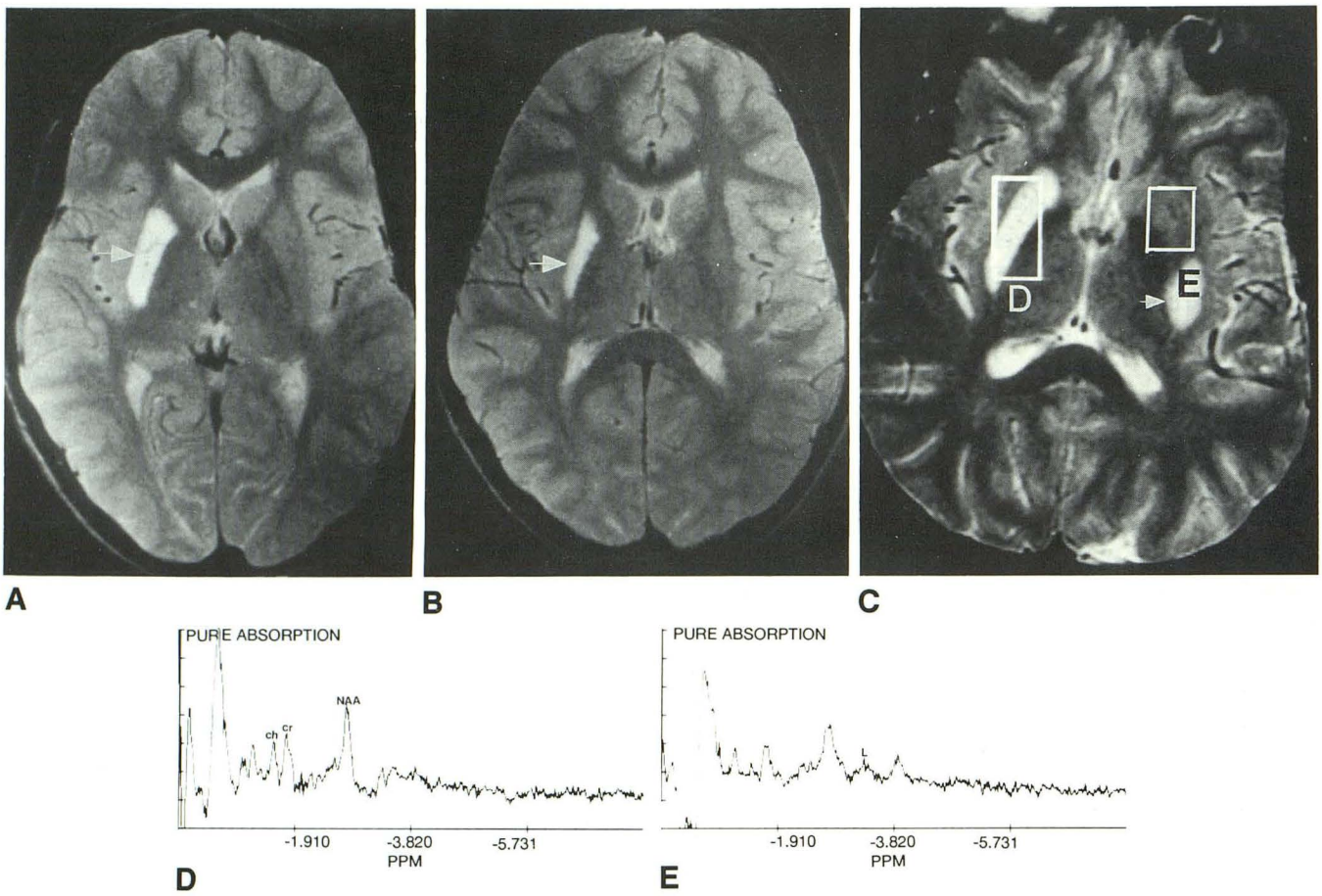


Fig. 2. Patient 4, with MELAS.

*A* and *B*, Axial SE 2500/80 images obtained at initial presentation (age 13 years). T2 prolongation is restricted to the right putamen (*arrows*).

*C*, Axial SE 2500/80 image obtained at the time of the new development of right body motor symptoms (age 17 years). A new area of T2 prolongation is present in the left posterior putamen (*arrow*). Box D is the location of the spectrum shown in *D* and box *E* is the location of the spectrum shown in *E*.

*D*, Localized proton MRS from the box labeled D in *C*. NAA, creatine/phosphocreatine (*cr*), and choline (*ch*) peaks are labeled. No discernible lactate peak is seen at 3.4 ppm.

*E*, Localized proton MRS from the box labeled E in *C*. NAA, creatine, and choline are less well seen, possibly because of tissue destruction or technical factors. A discernible doublet (*L*) is seen at 3.4 ppm, compatible with lactate. The source of the peak at 3.9 ppm is undetermined.

compose the mitochondrial electron transport chain are encoded for by mitochondrial DNA (mtDNA), whereas the genes for other component polypeptides are located in nuclear DNA (nDNA). The mitochondrial electron transport chain is composed of five molecular complexes (known as complexes I through V), which are constructed from 69 polypeptide subunits. Human mtDNA encodes 13 subunits; nDNA encodes 56 subunits (4, 5). The expression of the mtDNA genes requires their replication, transcription, and translation; most of the polypeptides for these processes are encoded by the nDNA (5). *Thus, oxidative phosphorylation* (step 4 in the steps of mitochondrial metabolism listed above) *requires hundreds of nuclear, mitochondrial, and cytoplasmic genes.* An extraordinary number of combinations of genetic defects are possible, all of which result in disturbed mitochondrial metabolism.

### *Genetic Considerations*

Mitochondria are the only subcellular organelles that contain their own DNA. In addition to the 13 polypeptides of the respiratory chain complexes mentioned previously, mtDNA encodes for the ribosomal RNA and transfer RNA needed for the translation of the DNA sequences (20).

**TABLE 2: Summary of imaging findings**

| |
|---|
| MELAS |
| Sulcal and ventricular prominence |
| Unilateral or bilateral posterior temporal, parietal, or occipital areas of hypodensity (CT) or long T1, T2 involving white more than gray matter (three patients) or isolated putaminal involvement (one patient) |
| MERRF |
| Diffuse sulcal and ventricular prominence |
| Calcified, shrunken globus pallidus |
| T2 prolongation in subinsular white matter, caudate nuclei |
| Small hippocampal formations |
| Kearns-Sayre syndrome |
| Diffuse sulcal and ventricular prominence |
| Prolonged T2 relaxation in subcortical cerebral white matter, cerebellar white matter, globi palladi, thalami, and substantia nigra |
| Leigh disease |
| T1, T2 prolongation in corpora striata, thalami, substantia nigra, inferior olivary nuclei, periaqueductal gray matter, cerebral cortex |
| Delayed myelination |
| Demyelination |
| Alpers disease |
| Diminished cerebral white matter |
| Delayed myelination |
| Cortical thinning, most prominent in posterior temporal, occipital, and frontal lobes |
| Menkes disease |
| Short T1 in involved cortex in early phases |
| Very rapid degeneration of all brain structures with profound atrophy and formation of subdural hematomas |

In the formation of the zygote, mtDNA is contributed exclusively by the oocyte, a process known as *maternal inheritance* (21). Although each human cell contains only two sets of nuclear genes (nDNA), each cell has hundreds of mitochondria and thousands of mtDNA genomes. Each time a cell divides, the mitochondria and mtDNAs are randomly segregated into the daughter cells. Thus, when a mutation affects some mtDNAs in the ovum or zygote, it will be passed on to subsequent generations of cells in a random manner. Some cells will have normal genomes (normal homoplasmy), some will have a mixed population of mutant and normal genomes (heteroplasmy), and some will have predominantly mutant genomes (mutant homoplasmy). The *severity of the oxidative phosphorylation defect* in a particular cell is a product of the nature of the mtDNA mutation and the proportion of the mutant mtDNAs within the cell. The *quality and severity of the patient's symptoms* depend upon the severity of the oxidative phosphorylation impairment within and the amount of energy required by the affected organs. Thus, as a result of the randomness of the distribution of the mtDNA, two siblings with the same inherited genetic defect will have different phenotypes that are dependent upon the relative concentrations of the mutant mtDNAs in various organs and the energy requirements of those organs (2, 5, 6, 25, 29).

As mentioned earlier, mtDNA encodes for only a small percentage of the total mitochondrial protein. Most mitochondrial proteins, including many involved in the replication of mtDNA, are encoded by nDNA, synthesized in the cytoplasm, and imported into the mitochondria (20); the production of these proteins is, therefore, controlled by autosomal inheritance (5, 30). Moreover, the importation of proteins from the cytoplasm into the mitochondria requires both energy and the formation of specific receptors (encoded by nDNA) on the mitochondrial surface (2, 20). Thus, *inherited mitochondrial diseases may result from any of a wide range of genetic errors with extremely variable inheritance patterns and variable phenotypic expression of the genetic errors.*

### *Consequences of Aging upon Mitochondrial Function*

Recent experimental work has revealed that the oxidative phosphorylation system (the electron chain transport system of the mitochondria) functionally declines with age in many organs (22, 23). One possible cause of this age-related decline in function is damage of mtDNA by oxygen free radicals, which are a natural by-product of oxidative phosphorylation (because electrons can be transferred directly from the reduced components of the electron transport chain to oxygen). It is estimated that 1% to 4% of oxygen uptake by our cells eventually become oxygen radicals (5). MtDNA seems especially susceptible to oxidative damage, accumulating 16 times more oxidative damage than nDNA (5), possibly because the rate of replication of mtDNA is 10 times that of nDNA (6) and because mtDNA lacks the ability to repair itself (31). As a result of this progressive diminution of mitochondrial function, *mitochondrial disorders may occur at any age, depending upon the rate of functional decline, the type of genetic defect, and the distribution of the genetic defect in various organs. Moreover, patients become progressively more affected as they age.*

### *Classification of Mitochondrial Diseases*

Some clinical features are characteristic of many of the mitochondrial disorders. Among

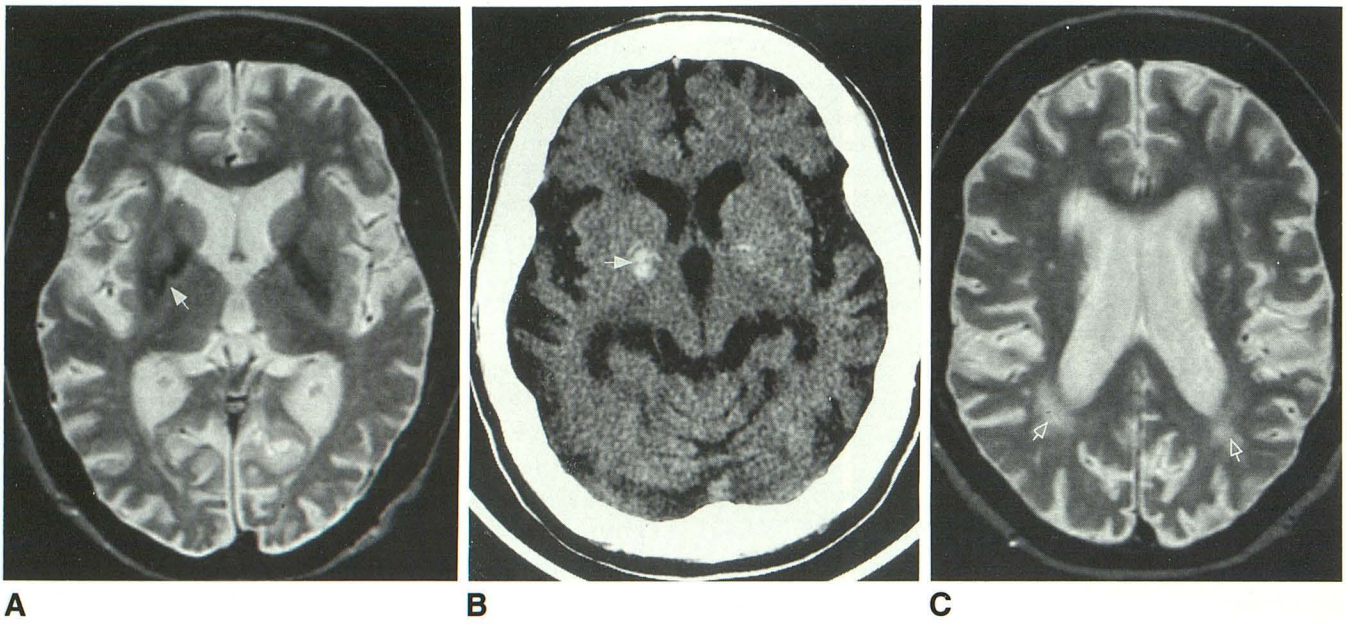


Fig. 3. Patient 6, with MERRF.

*A*, Axial SE 2000/80 image shows a diffuse loss of gray and white matter, with prominent sulci and large ventricles. The right globus pallidus (*arrow*) is distorted.

*B*, Axial noncontrast CT scan at the level of the lentiform nuclei shows that the distortion of the right globus pallidus in *A* was secondary to calcification (*arrow*). Less calcification is seen in the left globus pallidus.

*C*, Axial SE 2000/80 image at the level of the bodies of the lateral ventricles shows T2 prolongation (*arrows*) in the regions dorsal and superior to the trigones, which normally myelinate late.

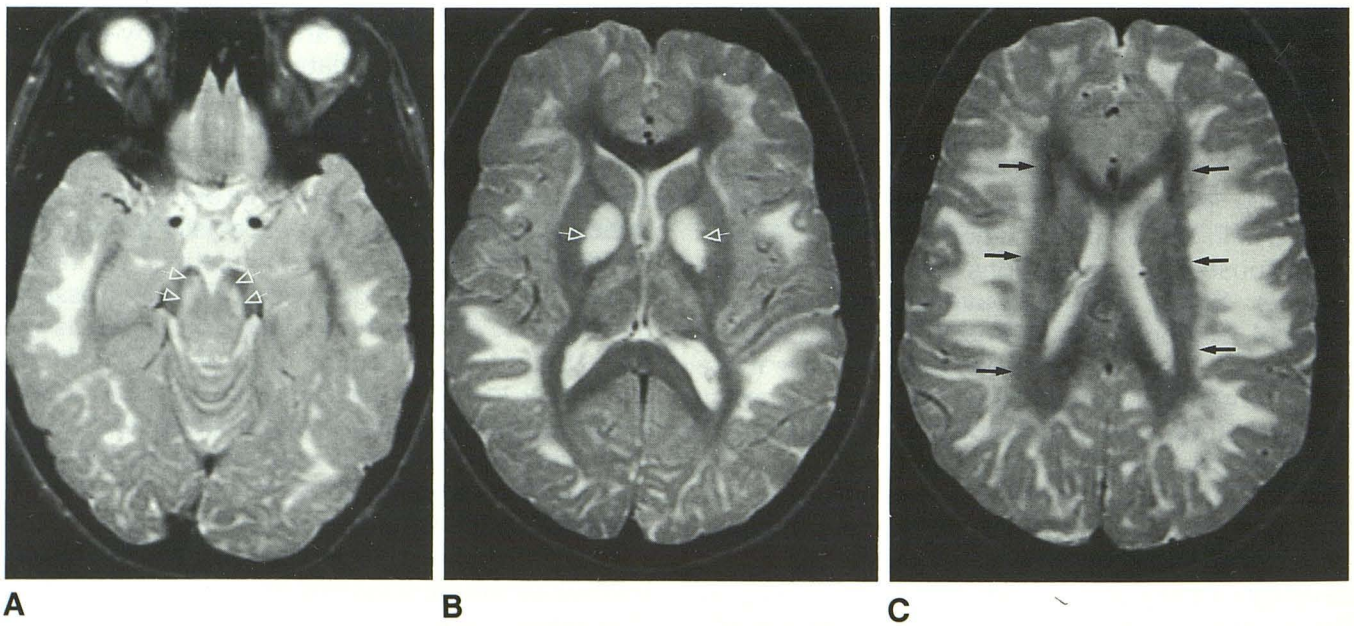


Fig. 4. Patient 6, with Kearns-Sayre syndrome.

*A*, Axial SE 3000/80 image shows T2 prolongation of the substantia nigra (*arrows*) and the peripheral temporal white matter.

*B*, Axial SE 3000/80 image shows T2 prolongation involving the globi palladi (*arrows*), the external capsules, and the peripheral hemispheric white matter. Note the lack of involvement of the periventricular white matter.

*C*, Axial SE 3000/80 image shows dramatic T2 prolongation of the peripheral hemispheric white matter with a stripe (*arrows*) of unaffected white matter around the lateral ventricles.

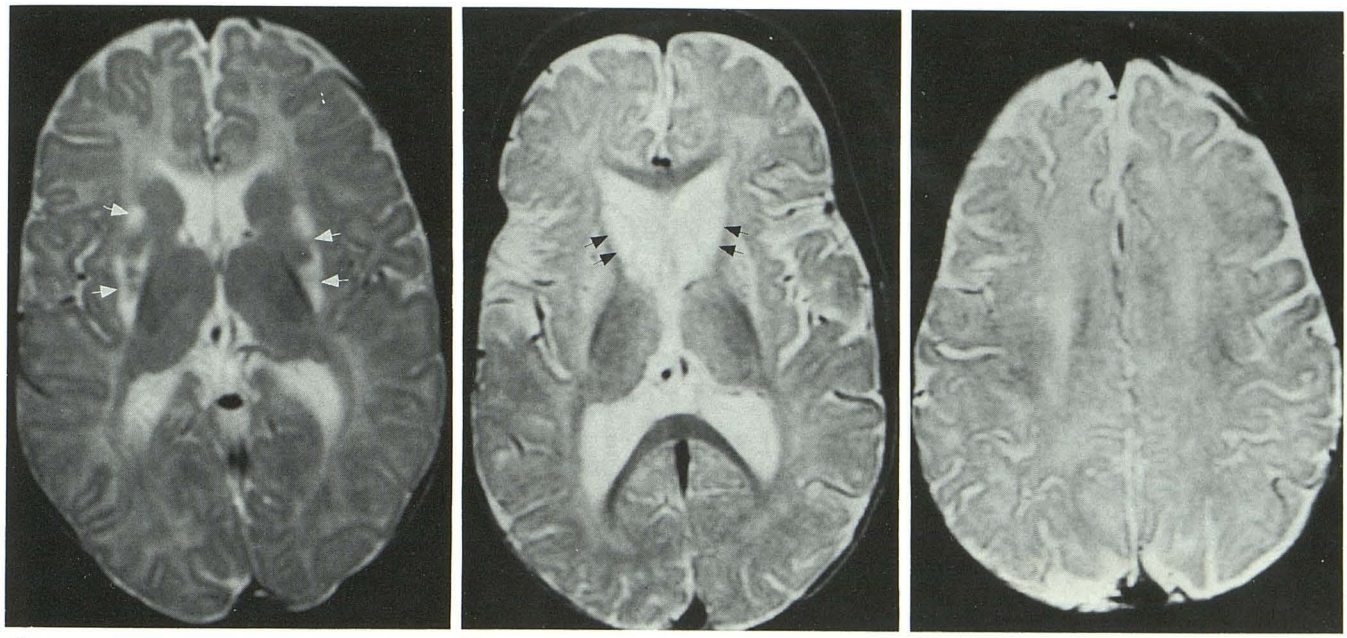


Fig. 5. Patient 14, with Leigh syndrome.

*A*, Axial SE 2800/90 image taken when the patient was 6 months of age shows patchy T2 prolongation (*arrows*) in the putamina bilaterally. Note the sparing of the caudate heads at the time of this examination.

*B*, Follow-up SE 2800/90 when the patient was 12 months of age shows the progression of putaminal involvement and new T2 prolongation involving the caudate heads (*arrows*). The ventricles and sulci have enlarged, indicating diffuse cerebral atrophy.

*C*, SE 2800/90 image from the scan when the patient was 12 months of age shows a lack of low signal in the corticospinal tracts, indicating delayed myelination.

these are seizures, short stature, mental deterioration, episodic headache, muscle weakness, exercise intolerance, and neurosensory hearing loss (2–4, 27). When these symptoms occur in patients who have the classic symptom complex of a specific mitochondrial disorder, a specific diagnosis (Table 3) is rather straightforward. However, when patients have the signs and symptoms limited to those listed above or signs and symptoms listed above in conjunction with others that are less classic, the differentiation between mitochondrial "syndromes" becomes blurred. Thus, some controversy exists concerning the classification of mitochondrial disorders. Two main schools of thought exist on this subject. One school (2, 5, 32) believes that certain clinical features are adequately clustered in some patients to allow the identification of several syndromes that are useful in patient management. The other believes that the overlap of features among the "syndromes" is too great to make the clinical classifications useful; this school awaits a biochemical/molecular genetic classification (3, 4, 17, 18). We acknowledge that considerable overlap occurs and that some patients have mitochondrial disorders that cannot be specifically classified (3, 4, 27, 33, 34). However, in view of the fact that considerable phenotypic heterogeneity exists, even among those with apparently identical genetic defects, we believe that a classification based upon clinical characteristics is useful in those cases in which it is possible. Therefore, we have attempted to classify our patients according to the best classification systems available (Table 3) (2, 5). The clinical, genetic, pathologic, and imaging characteristics of the specific syndromes will be discussed and compared with the findings in our patients before some general comments concerning our results are made.

## *MELAS*

MELAS refers to a group of disorders that are characterized by episodes of nausea, vomiting, and stroke-like events (hemianopsia and hemiparesis) in conjunction with some of the signs and symptoms of generalized mitochondrial disease (2, 6, 25, 29, 35–37). The stroke-like events may give rise to permanent or reversible deficits. Patients can seek treatment at any age, most commonly in the second decade of life (37).

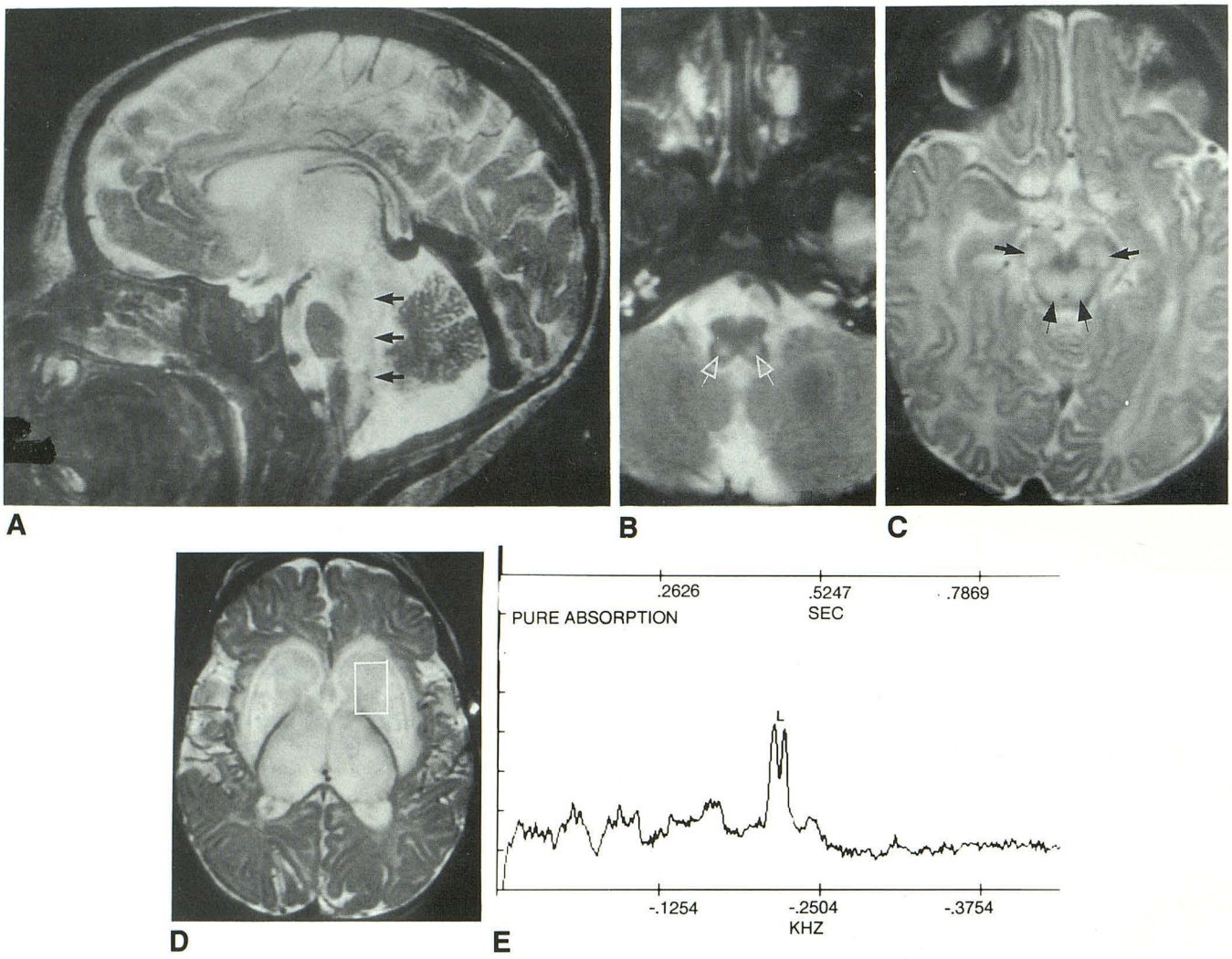


Fig. 6. Patient 9, a 3 month old with Leigh syndrome.

*A*, Sagittal SE 3000/120 image shows T2 prolongation (*arrows*) in the dorsal mesencephalon (*top arrow*), pons (*middle arrow*), and medulla (*bottom arrow*).

*B* and *C*, Axial SE 3000/120 images show T2 prolongation in the region of the medullary reticular formation (*open white arrows*), the periaqueductal region (*large vertical black arrows*), and the substantia nigra and red nuclei (*small horizontal black arrows*).

*D*, Axial SE 3000/120 image shows swelling and T2 prolongation involving the caudate heads, the lentiform nuclei, and the thalami. The *box* indicates the region from which the spectrum in *E* was obtained.

*E*, Proton MRS from the region indicated by the box in *D* shows an absence of the normal NAA, creatine/phosphocreatine, and choline peaks and the presence of a large doublet (*L*) at 0.2 kHz downfield from water, diagnostic of lactate.

Levels of lactate in the serum and cerebrospinal fluid (CSF) are usually elevated. Genetic studies have shown that some patients with MELAS have a point mutation in some of their mtDNA (5). Electron microscopy of cerebral blood vessels has shown swelling and a striking increase in the number of mitochondria in the smooth muscle and endothelial cells of pial arterioles and small arteries (38). This observation suggests that the cerebral ischemia is caused by exacerbations of the disease involving the blood vessels themselves.

Imaging studies show increased water in the affected areas of the brain, primarily in the parietal and occipital lobes (36, 39). Sequential scans may show resolution and subsequent reappearance of the abnormal areas (36, 39, 40). The lesions are not restricted to a specific vascular distribution. Three of the four patients with MELAS in our series showed parietooccipital hypdensity on CT and T2 prolongation on MR, similar to previous descriptions (Fig 1). We found that the cerebral cortex appeared relatively spared in two of the three patients, a fact that initially

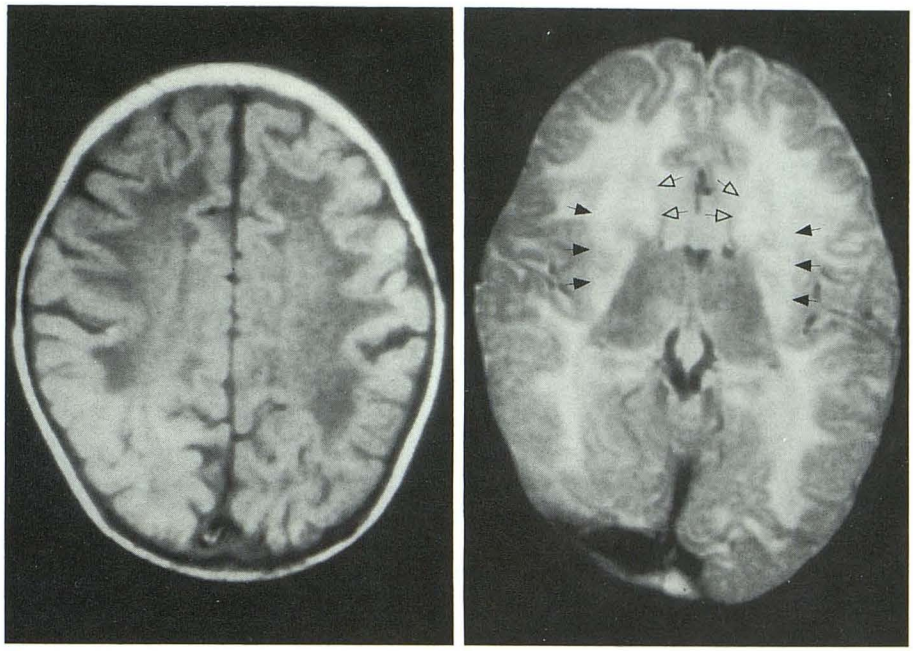


Fig. 7. Patient 11, an 11 month old with Leigh disease (proven at autopsy).

*A*, Axial SE 600/20 image shows a complete lack of the T1 shortening associated with myelination in the cerebral white matter. This appearance initially suggested the diagnosis of leukodystrophy.

*B*, Axial SE 2500/70 image shows abnormal T2 prolongation in the caudate heads (*open black arrows*) and in the lentiform nuclei (*closed black arrows*), as well as in the cerebral white matter.

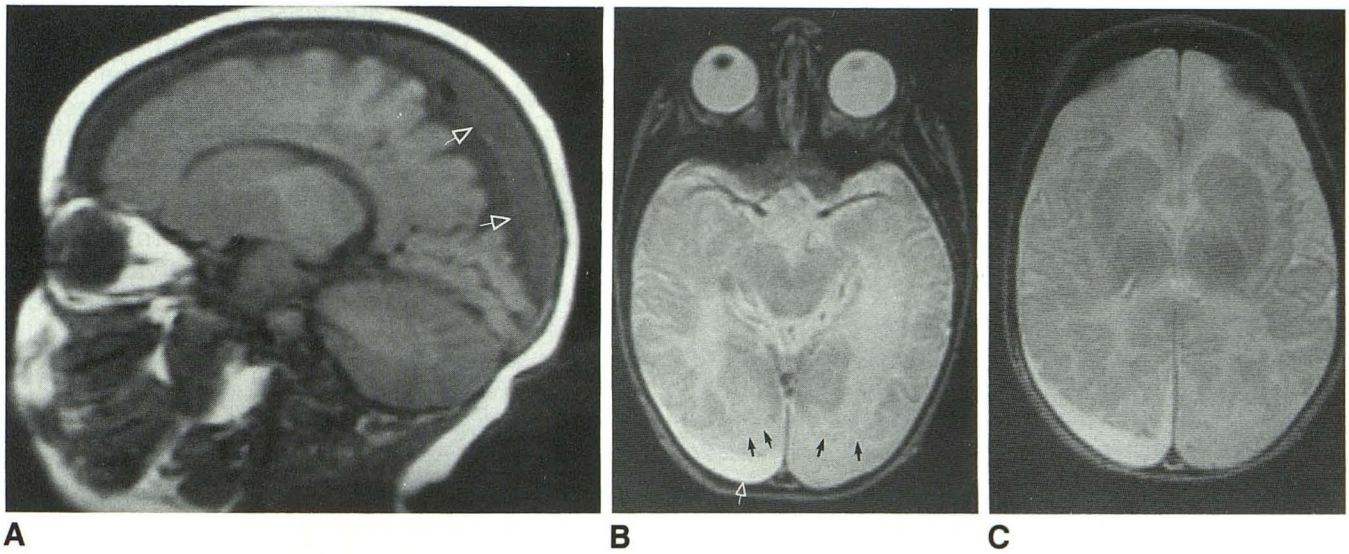


Fig. 8. Patient 16, a 4 month old with Alpers disease.

*A*, Right parasagittal SE 600/20 image shows less hyperintensity in the cerebral hemispheric white matter than expected for age, indicating delayed myelination. A subdural hematoma (*arrows*) is present.

*B*, Axial SE 2800/70 image shows cortical thinning (*black arrows*) in the occipital lobes bilaterally. The right subdural hematoma (*white arrow*) is hyperintense compared with the CSF.

*C*, Axial SE 2800/70 image shows a complete lack of low signal in the posterior limb of the internal capsule, diagnostic of delayed myelination. The right subdural hematoma is again noted, as is the cortical thinning in the frontal and occipital lobes.

obscured the diagnosis. MRS in two of these patients showed a high lactate level in the affected areas of brain (Figs 1D and E and 2E), a finding that has been described in other mitochondrial disorders (41, 42) and that was present in the brains of all five of the patients in our study on whom spectroscopy was obtained. However, because infarctions of any cause seem to result in local increases in lactate (43), the presence of lactate in a patient with the acute onset of neurologic deficit is certainly not specific for MELAS. Patient 4 (Fig 2) had an MR imaging pattern different from those of the other three in that the signal abnormalities were restricted to the putamina, thereby mimicking the MR appearance of Leigh disease or Leber hereditary optic neuropa-

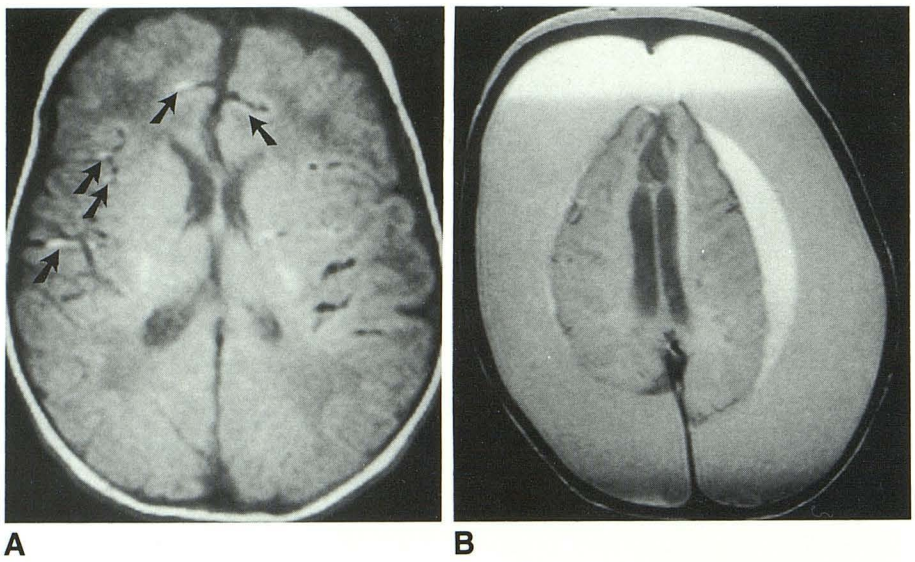


Fig. 9. Patient 19, with Menkes disease.

*A*, Axial SE 600/20 image when the patient was 1 month of age shows T1 shortening (*arrows*) in the cortex around the cingulate and sylvian sulci.

*B*, Follow up SE 600/20 image when the patient was 5 months of age shows profound atrophy with enormous bilateral subdural hematomas.

**TABLE 3: Phenotypic classification of mitochondrial disorders**

| |
|---|
| Exclusive or predominant muscle involvement |
| Fatal infantile myopathy |
| Benign infantile myopathy |
| Predominant brain involvement |
| Subacute necrotizing encephalomyelopathy (Leigh disease) |
| Alpers syndrome |
| MERRF |
| Trichopoliodystrophy (Menkes disease) |
| MELAS |
| Other |
| Progressive external ophthalmoplegia |
| 1. Isolated |
| 2. Retinitis pigmentosa and other organ involvement (Kearns-Sayre syndrome) |
| 3. Encephalomyopathy in adults |
| 4. Myoneurogastrointestinal encephalopathy |

Note—Modified from DiMauro et al (2).

thy (LHON) with dystonia (see below). Of interest, MRS of the chronically involved right putamen, in which the lesion was a minimum of 4 years old, did not show an enlarged lactate peak (Fig 2D), indicating that lactate may be slowly washed out of the tissue after active injury to the tissue ceases.

### *MERRF*

Patients with MERRF have many signs and symptoms similar to those of patients with MELAS. Patients have short stature, dementia, sensorineural hearing loss, easy fatigability, and elevated levels of lactate in the serum and CSF (2, 6, 29). They differ from patients with MELAS by the presence of myoclonus, seizures, and profound ataxia and by the absence of episodic vomiting, blindness, and episodes of hemiparesis/hemianopsia (44, 45). MERRF is characterized genetically by a mutation of mtDNA leading to deficiencies of complexes I and IV of the respiratory chain (5, 46). As a result, these patients display maternal inheritance and clinical manifestations are variable among maternal relatives and proportional to the percentage of mutant mtDNAs and the age of the affected individuals (44).

Imaging studies of patients with MERRF are nonspecific. The cerebral and cerebellar white matter are reported to show patchy low density on CT and patchy T2 prolongation on MR (47) (Fig 3), as were present in our two cases. Cerebral and cerebellar atrophy are almost always present (47). Involvement of the deep gray matter nuclei, as was present in one of our cases, has been reported pathologically, with degeneration and calcification of the cerebellar dentate nucleus and the globus pallidus (Fig 3A and B) being the most common manifestations (48). Because calcification of the globus pallidus is a common change in elderly patients, who are known to have progressively diminishing mitochondrial function (22, 23), its presence in younger patients with mitochondrial disorders may suggest that it is a result of mitochondrial dysfunction in both populations. Another interesting feature in our two cases was T2 prolongation in the regions dorsal and superior to the trigones (Fig 3C), an area that myelinates late (13). This point will be elaborated upon in the next section.

### *Kearns-Sayre Syndrome and Chronic External Ophthalmoplegia Plus*

*Kearns-Sayre syndrome* is a disorder with varying definitions, depending upon the source (2, 5, 6, 25, 49). Most authors require external ophthalmoplegia, onset before age 20, and retinitis pigmentosa as characteristics of the syndrome. Others require elevated protein levels in the CSF (50) or heart block (47, 49) for clinical diagnosis. Patients may also have ataxia, dementia, short stature, sensorineural hearing loss, endocrine dysfunction, elevated lactate levels in the serum and CSF, and muscle weakness (2, 5, 26, 50). Patients with chronic external ophthalmoplegia plus have ophthalmoplegia, ptosis, and myopathy with few or no other symptoms. Some authors claim that the two disorders are different expressions of the same underlying defect (18). This claim may, in fact, be supported by the findings that both diseases are usually sporadic and show deletion mutations of mtDNA that are believed to have occurred early in development (5, 51).

Imaging studies in Kearns-Sayre syndrome show involvement of the white matter and of the deep gray matter nuclei, particularly the globi palladi, the thalami, and the cerebellar dentate nuclei. CT scans show cortical and white matter atrophy, hypodensity of the cerebral and cerebellar white matter, and variable hypodensity or calcification of the basal nuclei (47, 52). It is not clear whether the calcification is the result of the primary disorder or the associated hypoparathyroidism that often accompanies the syndrome (53). MR scans are reported to show the same appearance that we observed in our patients (Fig 4), with T2 prolongation in the deep gray matter nuclei, particularly the thalami and the globi palladi, and patchy white matter involvement (47, 54). Of interest was the fact that the white matter involvement was predominantly peripheral, with early involvement of the subcortical U fibers and sparing of the periventricular fibers (Fig 4C). The subcortical region is involved only late in the course of most dysmyelinating diseases (55, 56), with the notable exception of Canavan disease. One explanation given for the predominant involvement of deep white matter early in the course of most inherited disorders of myelin is that the deep myelin forms early and the peripheral myelin forms later (57–59). In most "dysmyelinating diseases," such as the lysosomal and peroxisomal disorders, abnormal myelin is broken down by normal maintenance processes in the brain, with the older, central myelin being affected first (47, 56, 60–62). It is of interest to note that Canavan disease, which is now recognized to be the result of a deficiency of aspartoacylase (63), was originally classified by Shapira et al (64) as a mitochondrial disorder. Moreover, both mitochondrial disorders and Canavan disease are characterized by spongy degeneration of the white matter (65). However, 1) gray matter involvement is not seen in Canavan disease, 2) the patterns of white matter involvement are different from those in mitochondrial disorders, and 3) spongy myelinopathies from other causes also involve the subcortical white matter early (65). These factors clearly separate Canavan disease from the mitochondrial disorders on pathologic grounds. It appears, therefore, that disorders leading to spongy myelinopathy, whatever the cause, affect the newer white matter (peripheral and dorsal/superior to the trigones, as seen in the patient with MERRF) preferentially, or conversely, whatever processes result in the early involvement of newer white matter cause spongy degeneration.

### *Subacute necrotizing encephalomyelopathy (Leigh disease)*

Leigh disease is the name given to a complex of symptoms with characteristic, but variable, clinical and pathologic findings (8, 66). The typical presentation is of hypotonia, psychomotor deterioration, and dysfunction of the brain stem and basal ganglia, often resulting in ataxia, ophthalmoplegia, ptosis, dystonia, and swallowing difficulties toward the end of the first year of life. However, many different symptom complexes have been reported in conjunction with the characteristic pathology of cystic cavitation, vascular proliferation, neuronal loss, and demyelination in the midbrain, basal ganglia, cerebellar dentate nuclei, and occasionally, cerebral white matter (8, 33, 65, 67). Furthermore, a number of different biochemical and genetic abnormalities have been identified in patients with a clinical phenotype of Leigh syndrome. Among these are pyruvate dehydrogenase deficiency (68), pyruvate carboxylase deficiency (69), and cytochrome *c* oxidase deficiency (70). Many researchers, therefore, consider both Leigh disease (with the classical pathologic finding initially described by Dr. Leigh [66]) and Leigh syndrome (the characteristic combination of clinical features) to be the end result of a number of different defects affecting many aspects of mitochondrial function (2, 8, 26, 33, 67). Both neonatal onset and an

adult form of the disease have been reported (33, 67, 71). Most cases appear to be sporadic.

A number of publications have discussed the imaging findings in Leigh disease (7, 9, 72–76). Areas of hypoattenuation (CT) and prolonged T1 and T2 relaxation (MR) are seen, primarily in the putamena, globi pallidi, caudate nuclei, periaqueductal region, and cerebral peduncles, with occasional involvement of the cortical gray matter, subthalamic nuclei, restiform bodies, decussation of the superior cerebellar peduncles, and cerebral white matter. The dorsal pons seems to be affected in those patients with cytochrome *c* oxidase deficiency (76). MRS has shown decreased NAA and elevated lactate levels, with the lactate elevation most pronounced in those areas most severely affected on the imaging studies (41, 42).

MR imaging and MRS in our patients revealed findings similar to those discussed previously (7, 9, 41, 42, 72–76); however, a few new observations are worth discussing. The involvement of the dorsomedial medulla (Fig 6B) has not been reported as an imaging finding in Leigh disease, probably because the area is obscured by beam-hardening artifact on CT and by misregistration of moving CSF protons on MR without gradient moment nulling. We found prolonged T2 relaxation in this location in two patients.

Patient 11 had significant disease of the cerebral white matter (Fig 7); identification of the basal nuclei involvement was particularly important in establishing the correct diagnosis in his case. On the initial review of the films, the involvement of the corpus striatum was not appreciated, resulting in a working diagnosis of leukoencephalopathy. Appreciation of the corpus striatal abnormality aided in establishing the correct diagnosis.

The presence of lactate on localized MRS, although nonspecific, can also aid in making the diagnosis. The presence of bilateral putaminal or corpus striatal lesions containing elevated lactate levels (Fig 6D and E) in the absence of vascular disease (infarctions also have elevated levels of lactate [43]) is very suggestive of Leigh disease. However, as the MR imaging and MRS studies of patient 4 (with MELAS, Fig 2) demonstrate, the findings are not specific.

### *LHON*

LHON (77) is a disorder in which patients have a normal childhood but have an increased probability of going blind as they age. Vision is usually lost between the ages of 18 and 40 years (78). Males are predominantly affected, with a 60% to 90% predominance (78). The pathologic alteration appears to be axonal degeneration with demyelination of the central part of the optic nerves, chiasm, and tracts (79, 80). LHON is maternally inherited, caused by missense mutations in mtDNA. Four mutations that can cause visual loss have been identified (5). Five other mutations have been identified that can cause visual loss when present in combination; these latter mutations appear to have additive defects that eventually reduce oxidative phosphorylation sufficiently to affect vision (5). Although visual loss is usually the only manifestation of disease in these patients, some associations with neurologic abnormalities (hyperreflexia, ataxia, peripheral neuropathy [81], and dystonia [82, 83]), cardiac conduction abnormalities, and skeletal anomalies (78, 84) have been described. The association of dystonia and LHON has been reported in a large number of patients and may represent a separate disorder (83).

Few reports have described imaging findings in LHON. CT and MR scans are usually normal (85), although T2 prolongation in the optic nerves and tracts has been demonstrated by short TI inversion recovery MR sequences (86). Scattered areas of T2 prolongation in the cerebral hemispheric white matter have been reported in three patients (85, 87); however, these may be senescent changes or other nonspecific white matter abnormalities and are not definitively related to the disease. Patients with LHON and dystonia may show bilateral damage to the corpus striatum (82–84, 88), making them indistinguishable from patients with Leigh disease (Fig 5) and some cases of MELAS (Fig 2) by imaging. This group of patients probably has more complex genetic defects than simple LHON (78) or additional exogenous factors (84) contributing to their disorder.

MRS in LHON (89) has shown decreased PCr/Pi ratios on [$^{31}$P]MRS of the brain, indicating a decreased energy reserve, as would be expected in mitochondrial disorders. No reports of [$^{1}$H]MRS in LHON could be found.

### *Progressive cerebral poliodystrophy (Alpers disease)*

Alpers disease is a rare multisystem disorder characterized by predominant involvement of the cerebral gray matter and the liver (27, 65, 90–

92). The typical presentation is that of intractable seizures, particularly myoclonic jerks, following some early developmental delay or failure to thrive (27, 65, 92, 93). The onset of seizures often heralds a rapidly progressive course (92, 94). Onset is usually in the first few years of life, sometimes as early as the first few weeks. Although overt evidence of hepatic disease is variable, biochemical evidence is often present early in the course (92, 94). Pathologic studies show spongiform cortical atrophy, which is most pronounced in the occipital region, and atrophy of the basal nuclei, particularly the thalami and globi palladi, with reactive gliosis (47, 65, 92). Some debate exists as to whether hepatic involvement is necessary for diagnosis (65). Biochemical abnormalities associated with Alpers disease include cytochrome *c* oxidase deficiency (95), pyruvate cocarboxylase deficiency (96), and deficiencies of mitochondrial electron transport chain complex I (28).

Imaging analyses of patients with Alpers disease are few. Reported CT findings include focal hypodensities of both gray and white matter, followed by diffuse atrophy (27, 47). Others note that the low-density regions are more frequently in the posterior temporal and occipital lobes and involve both gray and white matter (92). The MR of our patient showed diminished white matter, delayed myelination, and cortical thinning that was most severe in the frontal, posterotemporal, and occipital lobes (Fig 8). No reports of MRS in Alpers disease could be found.

### *Trichopoliodystrophy (Menkes disease)*

Menkes disease (97) is an X-linked recessive disorder in which mitochondrial dysfunction is a result of the impaired intestinal absorption of copper (2). Low copper levels impair cytochrome oxidase activity, because cytochrome *c* contains two copper atoms (65). Although Menkes disease is technically not a primary mitochondrial disorder (because the mitochondria are affected secondarily), the patients exhibit many characteristics of mitochondrial disorders such as "ragged red fibers" on muscle biopsy (98) and abnormal mitochondria on electron microscopic studies of the brain (99). Therefore, we have chosen to include these patients in our study.

The three patients in our series with Menkes disease were typical in that they first had symptoms in infancy with hypotonia, hypothermia, failure to thrive, and seizures (65, 97). Head circumference at birth may be normal or decreased; a reduction with respect to the normal growth curve becomes evident. Patients have coarse, stiff, sparse hair with broken, nodular, frayed ends (65, 97); hence, the disease is referred to as "kinky hair disease." Most patients die before the second year of life.

A pathologic examination of the brains of patients with Menkes disease shows diffuse atrophy of the cerebral and cerebellar hemispheres. The cerebral arteries are thin walled and tortuous, secondary to anomalies of the elastic membrane and intimal cleavage (65). Microscopic examination shows widespread spongiform degeneration of the gray matter, sometimes exhibiting frank cavitation. Ferrugination of nerve cells is common (65). The volume of white matter is reduced, and the white matter is hypomyelinated (65).

Radiologic studies of Menkes disease have emphasized cerebral atrophy, the presence of large subdural collections, and tortuosity of cerebral blood vessels (16, 100–102). More recently, the rapid progression of the atrophy has been observed (102–104). We also observed the rapid progression of atrophy involving all structures of the brain on sequential scans over the period of a few months (Fig 9). Moreover, we observed short T1 and T2 relaxation times in the brains of two of our patients at various stages of the disease and wonder whether we may be observing a manifestation of ferrugination. An important point in this respect is that rapid brain atrophy in the presence of large bilateral subdural hematomas and apparent cortical blood is not necessarily a manifestation of asphyxic or physical trauma.

### *Significance of MR and MRS Findings in Mitochondrial Disorders*

As would be expected from a group of diseases with such diverse clinical and pathologic manifestations, the mitochondrial disorders have diverse findings on imaging studies, as well. A few important observations emerge from this study, however, that can be applied to mitochondrial disorders, in general.

1) Mitochondrial disorders should be thought of as diseases that primarily affect the gray matter. The initial imaging findings in most cases are of cortical atrophy or abnormal signal in the cortex or basal nuclei. When white matter abnormalities are present, they are almost always superimposed upon gray matter pathology.

2) When the white matter is involved, the newer

(subcortical and dorsal to the trigones) white matter is involved early in the process. As discussed earlier, most inherited disorders of myelin, such as the lysosomal and peroxisomal disorders, affect the (older) central white matter first and the (newer) subcortical white matter only in the later stages of the disease (47, 56, 60–62). Diseases that affect the subcortical white matter early in their course seem to be characterized by spongiform changes pathologically; this pattern of white matter involvement may be useful in radiologic diagnosis.

3) Although many similarities can be found among the mitochondrial disorders affecting older children and adults (MELAS, MERRF, Kearns-Sayre, progressive external ophthalmoplegia plus, LHON) and among those affecting infants and young children (Alpers, Menkes, Leigh), considerably fewer similarities can be found between these two groups. The first group is characterized by slowly progressive symptoms with a long period of normal development, whereas the second group becomes symptomatic acutely and profoundly, often at a very young age. These different courses almost certainly reflect different degrees of hereditary impairment of mitochondrial function. They may justify separation of mitochondrial disorders into two major clinical groups.

4) The value of MRS in mitochondrial disorders is still not established. The findings of elevated lactate levels and decreased NAA levels are nonspecific; they are seen in tumors (105), neuroaxonal dystrophy (41), Cockayne disease (41), and infarctions (43), as well as in mitochondrial disorders (41, 42). Certainly, finding elevated levels of lactate in apparently uninvolved brain, as reported by Detre et al (42), may be a useful sign of mitochondrial disease, when present. However, we observed elevated lactate levels in an area without T2 prolongation in only one of our patients. It is possible that future studies will reveal characteristic peaks (other than lactate) that enable a definitive diagnosis of mitochondrial disorders, especially if the signal-to-noise ratio and, hence, the resolution of specific peaks, can be improved by the use of higher-field-strength scanners.

5) Although imaging findings of deep gray matter involvement can allow one to suggest that the disorder affecting the brain is of mitochondrial origin, they are nonspecific and, in fact, do not even allow distinction among the different mitochondrial disorders. In this series, one patient with MELAS had MR findings identical to those of two patients with Leigh syndrome. MR findings described in LHON with dystonia are identical, as well. Bilateral involvement of the corpus striatum has also been described in methylmalonic acidemia (106), glutaric aciduria type II (6), hemolytic uremic syndrome (107), Wilson's disease (9), and cytoplasmically inherited striatal degeneration (88). Thus, the diagnosis of mitochondrial disorders is made by a combination of clinical presentation, imaging findings, and laboratory analysis.

## Summary

In this article, we have presented imaging findings of 19 patients and the MRS results of 5 patients with mitochondrial disorders. In addition, we have discussed some of the issues and controversies of mitochondrial disorders, a group of diseases that is still in the process of being defined and classified. These disorders have somewhat distinctive imaging patterns, including primary involvement of the gray matter and, when the white matter is involved, early involvement of the newest (peripheral) white matter, which allows distinction from most other disorders, both hereditary and acquired. In vivo MRS findings, although abnormal in all patients studied, appear to be nonspecific and less useful than imaging at this stage of spectroscopy development.

## Acknowledgment

The authors thank Chip Truwit, MD, for donating scans and information about patient 6, Rob Sevick, MD, for donating data about patient 5, and F. Chaney Li for donating imaging and clinical information about patients 16 and 17 to this project.

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